Prolonged Fever and Severe Hypercalcemia Revealing Systemic Extra-Pulmonary Sarcoidosis: A Lesson to be Learned

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Abstract

In sarcoidosis, isolated extra-pulmonary lesions are rare, and in such cases, the diagnosis can be very challenging. We hereby present a case of a 43-year-old woman who presented with prolonged fever, deep lymph nodes, massive splenomegaly, hepatomegaly and severe hypercalcemia, mimicking malignancy. The diagnosis of sarcoidosis was established after the failure of anti-tubercular therapy, the exclusion of differential diagnosis and the subsequent apparition of cutaneous sarcoids. This case highlight isolated extra-pulmonary pseudo-tumoral presentation of sarcoidosis resulting in longer diagnosis delay.

Keywords: Sarcoidosis; Hypercalcemia; Prolonged Fever; Granuloma; Sarcoïd.

Introduction

Sarcoidosis is an inflammatory multisystemic disease of unknown origin. It is characterized by the presence of noncaseating granulomas. In more than 90% of cases, sarcoidosis involves the pulmonary tissue and can associate lesions in other organs.[1] Isolated extra-pulmonary lesions are rare, and therefore the diagnosis of such forms can be very challenging.

We hereby present a case of a 43-year-old female patient who presented with prolonged fever, a malignant hypercalcemia, and a massive splenomegaly mimicking neoplastic condition and for whom the diagnosis of sarcoidosis was confirmed after a long delay.

Case Report

A 43-year-old Tunisian woman was referred to our department to explore a 5-month history of vomiting, anorexia, constipation and a 16-kg weight loss. The physical examination found an altered patient with high fever. Abdominal examination showed an enlarged firm spleen that was palpable below the umbilicus as well as a firm hepatomegaly. The laboratory tests showed hypercalcemia of 3.25 mmol/L (2.25-2.62 mmol/L), and a pancytopenia with microcytic anemia at 8.6 g/dL (12-16 g/dL), leucopenia at 3730/mm^3 (4000-10000/mm^3), lymphopenia at 620 /mm^3 (1500-4000/mm^3) and thrombocytopenia at 135000 /mm^3 (150000-450000/mm^3). Neutrophil polynuclear count was at 2420/mm^3 (1500-7000/mm^3). Ferritin level was at 105 ng/mL (20-200 ng/mL). Laboratory evidences of inflammation were noted: ESR at 85mm and C-reactive protein at 46 mg/L (<8 mg/L). Serum protein electrophoresis showed a polyclonal hypergammaglobulinemia at 28.8 g/L (9-13.5 g/L). Renal and hepatic functions were within normal range. Computed tomography (CT) of the thorax, abdomen and pelvis showed a multiple enlarged homogenous mediastinal and abdominal lymph nodes, hepatomegaly of nearly 22 cm, and a massive homogenous splenomegaly of 23 cm.

In order to treat the hypercalcemia, the patient received intravenous fluids and 20 mg per day of oral prednisone, which allowed lowering the calcium blood level to less than 2.5 mmol/l within the next few days.

Hispathological examination of 10 mediastinal lymph nodes showed a tuberculoid lymphadenitis with multiple non-caseating granulomas and no evidence of malignancy. Although the tuberculin skin test was negative, we decided to initiate the anti-tubercular national protocol treatment: 2 months HRZE (isoniazid-rifampin-pyrazinamide-ethambutol) followed by 4 months HR. This was justified given the high prevalence of this disease in our country and the existence of high fever.

Six months later, the clinical status of the patient was steadily worsening. The physical examination found a more enlarged spleen and multiple erythematous maculo-papular lesions in the arms (figure 1a), the back (figure 1b) and the neck similar to cutaneous sarcoidosis. Laboratory tests showed a microcytic anemia with no leucopenia nor thrombocytopenia. Ferritin level decreased to 22 ng/ml. The biologic inflammatory syndrome slightly decreased (ESR: 45 mm CRP: 8.8 mg/L). Calcemia was within normal range. Polyclonal hyper gammaglobulinemia was relatively stable at 24.2 g/l. The skin biopsy revealed a non-caseating granuloma suggestive of sarcoidosis. CT scan showed an increase in the number and the volume of the mediastinal lymph nodes, the splenomegaly raised to 26 cm and the hepatomegaly to 25 cm. Further investigation showed also an angiotensin-converting enzyme (ACE) level at 106 U/L (normal range 20-70 U/L). Upon all the new data, the anti-tubercular treatment was discontinued. The diagnosis of sarcoidosis was confirmed and the patient was given oral corticosteroids at a dosage of 1mg/kg/day with a significant amelioration in the clinical and biological status within the next few weeks. An abdominal echography performed at 6 weeks of treatment showed a decrease in the spleen and the liver size (19 cm for both). A CT-scan performed at 6 months found a complete regression of the splenomegaly and the hepatomegaly.

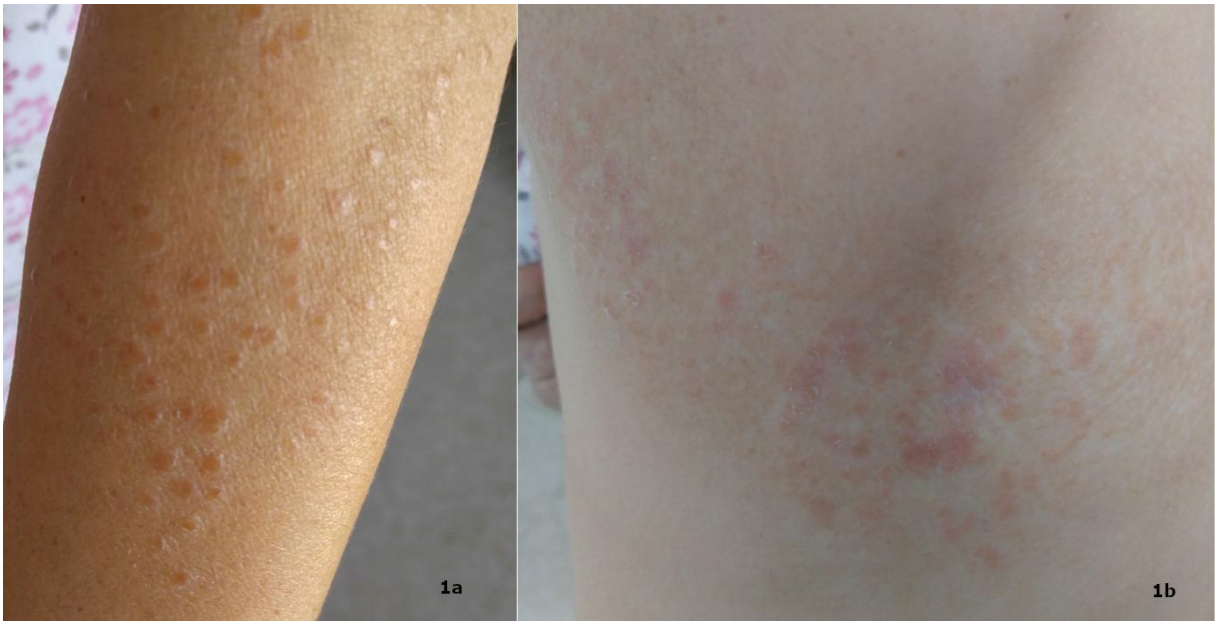

Figure 1: (a) Erythematous maculo-papular lesions in the arms related to cutaneous sarcoids. **(b)** Erythematous maculo-papular lesions the back related to cutaneous sarcoids.

Discussion

Sarcoidosis is a chronic granulomatous disease that can involve all organs with different rates. The three criteria for diagnosis are: clinical and radiological presentation, evidence of non-caseating granulomas and evidence of no alternative disease.[2] These criteria enhance the fact that sarcoidosis present a very heteregenous group of clinical and radiological manifestations depending on the organs involved and can therefore mimick a large number of other granulomatous diseases.

Our observation is distinguished by a prolonged fever in a context of profound deterioration of the general condition associated with significant hypercalcemia and a clinical tumor syndrome. Apart from Lofgren syndrome, fever may be present in up to 10% of affected patients, particularly those with extensive involvement of retroperitoneal lymph nodes, liver or spleen involvement.[3,4] In our patient, the prolonged fever can be explained by, on the one hand, significant lymph node involvement in the abdominal area and significant hepatomegaly and splenomegaly.

Clinical hepatosplenic involvement is infrequent. In some cases, left upper abdominal pain with systemic symptoms including malaise, fever, fatigue and weight loss like in our patient, can be found.[1] Palpable clinical splenomegaly is uncommonly found in 2 to 42% of cases.[1] Furthermore, massive splenomegaly below the umbilicus like in our observation is only described in case reports because of its rare occurrence.[5] Hypersplenism with anemia and thrombocytopenia like in our patient is also rarely found, so is splenic rupture.[1,2,5-7]

In our case, the significant hepatomegaly was not associated with a disturbance of the liver function tests and could not oriented etiological diagnosis.

Unlike hypercalciuria which is a classic sign in sarcoidosis, hypercalcemia is less common and usually occur in 5% of cases.[8] But, it can reach up to 25% of cases in some studies.[8] A significantly high calcemia like in the range of patient's level is exceptional.[9]

In our situation, lymph node biopsy exclude malignancy and tuberculosis remains the main differential diagnosis. Indeed, tuberculosis is frequent in our country and could explain the associated hypercalcemia.[10] That's why anti-tubercular treatment was administrated.

In a further stage, the lack of efficacy of the antitubercular treatment and the later appearance of the skin sarcoids enabled us to confirm the diagnosis of sarcoidosis and to start the appropriate treatment. The good outcome with corticosteroid treatment was the final definite argument supporting the diagnosis of sarcoidosis.

Conclusion

Although sarcoidosis is not a classic etiology of prolonged fever associated with severe hypercalcemia and clinical tumor syndrome, this diagnosis should be considered in the presence of granuloma without caseous necrosis after formal elimination of tuberculosis.

Disclosure

No conflicts of interest.

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